REMARKS

Claims 13-17 are currently pending in the application. Reconsideration in view of the following remarks is respectfully requested.

Claim 13 is amended above to recite a "functional" TSH receptor. Support for the amendment can be found throughout the specification and in claim 15. The term "functional" means that the human TSH receptor used for affinity purification behaves like the naturally occurring human TSH receptor in that it binds TSH and the broad spectrum of autoantibodies that appear in GD patient sera, autoantibodies that are known to bind conformational epitopes (see Morris et al. page 294, sentence bridging columns 1 and 2).

Rejection of Claims Under 35 U.S.C. §103

Claims 13-17 are rejected under 35 U.S.C. §103 as being unpatentable over Bergmann et al. (WO98/26294) as evidenced by U.S. 6,537,760 (hereinafter, the '760 patent), which is the U.S. national stage filing of the PCT international application, in view of Morris et al. According to the Office Action, Bergmann et al., in addition to teaching a method for the detection of TSH receptor autoantibodies by contacting a biological sample with TSH receptor that is immobilized on a solid support in the presence of a labeled "primary competitor" to competitively bind to the TSH receptor, contemplated the use of labeled autoantibodies as the primary competitor. Furthermore, the Office Action asserts that, even though the '760 patent does not disclose affinity purification of the autoantibodies, one of skill would have been motivated to affinity purify the autoantibodies prior to use in a detection assay, particularly in view of Morris et al. Applicants respectfully disagree.

The present invention is directed to a method for determining the amount of all anti-TSHR autoantibodies (hereinafter TRab) in patients with thyroid autoimmune diseases, such as Graves' disease. The objective of the method is to be able to detect the entire spectrum of anti-TSHR autoantibodies that occur in these diseases, including stimulating autoantibodies, blocking autoantibodies and autoantibodies with no obvious effect, thereby providing a diagnostic tool that can identify ***any*** thyroid autoimmune disease patient. It is Applicants' position that, given the

diversity of TRab, one of skill in the art would not, based on the lack of any guidance in the teachings of the cited references or elsewhere in the prior art with respect to an appropriate affinity purification scheme have had an expectation of success in arriving at the precise affinity purified autoantibody preparation which Applicants obtained having unexpected accuracy and reliable results.

Applicants' claimed method utilizes a preparation of affinity-purified autoantibodies derived from the sera of Graves' Disease patients. The method of affinity purification is extremely important in that it ultimately determines the specificity of autoantibodies in the detection preparation. The method for the affinity purification of the claimed autoantibody preparation is disclosed in the specification beginning on page 17, line 29 and continuing on page 18. The solid phase material to which the GD sera will be contacted has functional TSHR bound to it by a specific monoclonal anti-TSHR antibody, BA8,that recognizes the native hTSHR without interfering with binding of TSH or TRab. Thus, the full spectrum of autoantibodies that exist in the sera of GD patients, stimulating autoantibodies, blocking autoantibodies and no-effect autoantibodies, can be affinity purified from GD sera for use as detection antibodies.

Neither of the cited references, either individually or in combination teach or fairly suggest the affinity-purified autoantibodies used in Applicants' claimed method.

U.S. 6,537,760

The specification of the '760 patent clearly sets out the significance of the heterogeneous nature of TSHR autoantibodies and the difficulty in developing a reliable assay which accounts for all autoantibodies types.

> "It has long been known that heterogeneous autoantibody populations of different compositions are formed in autoimmune disease of the thyroid. The stimulating autoantibodies and the autoantibodies competing with TSH are only partly identical, i.e. there are stimulating autoantibodies which do not compete with TSH and there are also autoantibodies competing with TSH which do not have a stimulating effect. In addition, autoantibodies which neither have a stimulating effect nor compete with TSH may also be present (citations omitted). As a consequence of this, autoantibodies are detectable with the aid of radio receptor assays only in about 80-90% of patients suffering from Graves' disease

(citations omitted.)" (col.2, lines 29-45)"

Furthermore, though the term "autoantibodies" appears at col. 9, lines 7-13, the use of that term is clearly inconsistent with the rest of the teachings of the '760 patent, particularly the Description of the Experiments, which clearly anticipates the use of a "first competitor," labelled TSH and the use of a "secondary competitor," a monoclonal or polyclonal antibody directed against a peptide containing amino acids 20 to 39 of the complete, functional human TSH receptor.

Taken as a whole, Applicants urge that the '760 patent does not actually teach the use of "labeled autoantibodies." Nor does the '760 patent teach or provide any quidance with regard to the preparation or use of affinity-purified autoantibodies from the sera of GD patients.

Morris et al.

Morris et al. confirms the diversity that exists among anti-TSHR autoantibodies in Graves' disease (GD) patients. Using a series of overlapping peptides derived from the sequence of the entire extracellular domain of the human TSH receptor, Morris et al. identified three peptides, 376-394, EC3 and 181-200, that were recognized by the majority of patients. In only two peptides, however, did the overall results reach statistical significance when compared to controls (p. 290, left col. last line).

Morris et al. then used the three peptides to affinity purify TSHR autoantibodies from the sera of four GD patients. Not surprisingly, the results differed from patient to patient reflecting the diversity of autoantibody types in each patient: thyroid stimulating activity was enriched in the bound fraction from at least two of the three peptide affinity columns in each of the four patients, although the pattern of affinity enrichment differed between patients. One patient was found to possess a combination of stimulatory and inhibitory TSHR antibodies and, after affinity purification, the anti-376-394 and anti-EC3 fractions were enriched in stimulatory activity, suggesting that those regions of the receptor were epitopes for stimulatory antibodies, whereas the anti-181 fraction had potent inhibitory activity.

Morris et al. does not teach or suggest the use of these affinity-purified autoantibodies from GD patients for use in a diagnostic assay for the detection of the full spectrum of autoantibodies, nor would one of skill in the art conclude that they would be useful in identifying the full spectrum of autoantibodies in GD patients. For one thing, Morris et al. is using peptides, therefore, linear epitopes, to affinity purify autoantibodies from patient sera. In contrast, Applicants' autoantibodies, which are known to bind conformational epitopes, are affinity purified with a functional TSHR. The autoantibody population obtained by Morris et al. is not the same as Applicants' autoantibody preparation nor would one expect to obtain a similar preparation based on the distinctly different affinity purification methods.

Morris et al. concludes:

> "From the examination of our data, we conclude that the eliza technique used in [sic] these peptides has little or no utility in the clinical setting. The overall frequency of positive results, low reactivity of the IgG's, lack of correlation with clinical features, and cumbersome nature of the assay would severely limit its value in the diagnosis of autoimmune thyroid disease. Further, many of the antibodies identified by this technique may have little or no functional activity.

Furthermore, subsequent attempts by others to use anti-TSHR monoclonal antibodies either individually or in combination were unsuccessful in achieving acceptable results. (see Minich et al., *Antibodies to TSH-receptor in thyroid autoimmune disease interact with monoclonal antibodies whose epitopes are broadly distributed on the receptor*. Clin. Exp. Immunol. 136: 129-136 2004) Minich et al. used high affinity murine monoclonal antibodies directed to three sites of the TSHR ectodomain. The specific binding was inhibited by a proportion of sera from patients with GD containing TBII and TSAb or patients with autoimmune hypothyroidism containing TBII and TBAb, but no inhibition was seen by sera from patients with autoimmune thyroid disease, which were TBII negative and negative for TSAb or TBAb. Using a mixture of all three tracer mabs, did not increase the sensitivity in the GD or AIT group, compared to the best single mab alone. (Minich et al. page 132, bottom of col. 1)

The teachings of Morris et al. do no compensate for the deficiencies in the teachings of the '670 patent. Applicants' approach to developing an accurate diagnostic method by using labeled anti-TSHR autoantibodies affinity purified from GD sera for the detection of anti-TSHR autoantibodies is not taught or fairly suggested by the cited references and is therefore, novel and nonobvious. Applicants' affinity purification scheme including the particular choice of the anti-TSHR monoclonal antibody, BA8, that tethers a functional TSH receptor to the affinity purification solid phase resulted in unexpected results.

Withdrawal of the rejection under 35 U.S.C. 103 is respectfully requested.

Rejection of Claims for NonStatutory Obviousness-type Double Patenting

Claims 13-17 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. 6,537,760 (the "'760 patent"). In view of Applicants' remarks above that the claims are not obvious under 35 U.S.C. 103 in view of the '670 patent, a rejection based on nonstatutory obviousness-type double patenting cannot stand.

Withdrawal of the rejection is respectfully requested.

There being no other outstanding issues, it is believed that the application is in condition for allowance, and such action is respectfully requested. Should the Examiner believe that anything further is desirable in order to place the application in better condition for allowance, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

The undersigned hereby authorizes the Commissioner to charge any fee insufficiency and credit any overpayment associated with this submission to Deposit Account No. 08-1935.

Respectfully submitted,

Date: April 19, 2011

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